REMARKS

The title of the application has been amended in response to the Examiner's directive to provide a title that is more descriptive of the claimed invention. The amendment to the title does not constitute new matter.

Claims 1-44 were pending in this application. In view of their withdrawal from consideration, claims 2, 16, 18-22, and 33-43 have been canceled without prejudice. Claims 1, 3-15, 17, 23-32, and 44 have also been canceled without prejudice. Applicants reserve the right to pursue the subject matter of the canceled claims in a related application. New claims 45-82 have been added to more particularly point out and distinctly claim that which Applicants regard as the invention. The new claims are fully supported by the specification as filed, *see, e.g.*, page 2, lines 7-18; page 4, Table 1; page 7, lines 5-17; page 7, lines 18-22; page 7, lines 22-24; page 8, lines 5-8; page 8, lines 8-10; page 8, lines 30-34; page 8, line 11 to page 9, line 10; page 9, lines 4-6; page 9, lines 32-35; page 10, lines 1-4; page 10, lines 18-23; page 10, line 18 to page 11, line 10; page 11, lines 4-10; page 11, lines 27-31; page 24, lines 25-30; page 39, lines 27-31; page 43, lines 3-6; page 43, lines 20-21; page 45, lines 14-15; page 53, line 27 to page 57, line 35; page 54, line 16 to page 55, line 14; page 54, line 23; page 58, lines 1-22; page 63, lines 12-27; page 67, lines 3-13; page 68, lines 6-22; page 70, lines 12-23; page 72, lines 7-9; page 73, lines 3-6; page 76, line 29 to page 77, line 7; page 80, lines 28-30; and page 89, lines 1-8 of the specification. Thus, the new claims do not constitute new matter. Upon entry of this Amendment, claims 45-82 will be pending.

Applicants note that a Supplemental Information Disclosure Statement, a revised PTO-1449 form listing references A01 to A150, B01 to B70 and C01 to C226, and references A01 to A03, B01 to B70 and C01 to C226 listed on the revised PTO-1449 form were filed by Express Mail in the United States Patent and Trademark Office on September 8, 2004. Applicants respectively request that the Examiner enter and consider the references listed on the revised PTO-1449 form filed on September 8, 2004 as well as the references listed on the revised PTO-1449 form filed herewith.

Applicants respectfully request consideration and entry of the amendments and remarks made herein into the record for the present application.

I. THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 1, 3, 8, 9 and 11 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner contends that the claims are indefinite because the recitation of the terms "MEDI-507" and "LO-CD2a" do not clearly define the antibodies encompassed by the terms. In order to expedite prosecution and without conceding to the propriety of the rejection, Applicants have canceled claims 1, 3, 8, 9 and 11, without prejudice and added new claims 45-82. For the reasons detailed below, the rejection should not be applied to new claims 45-82.

Applicants respectfully assert that one of skill in the art would have been able to ascertain the antibodies encompassed by the terms "MEDI-507" and "LO-CD2a." The specification of the present application teaches that MEDI-507 is disclosed in International Publication No. WO 99/03502 ("Bazin"), which has been cited as prior art by the Examiner, and U.S. application Serial No. 09/462,140 (now issued U.S. Patent No. 6,849,258) and incorporates these references into the specification. *See* page 64, lines 29-31 of the specification of the present application. Example 11 of Bazin describes the construction and analysis of MEDI-507. Figures 31 and 42 of Bazin provide the amino acid sequences for the light chain variable region and heavy chain variable region of MEDI-507. Thus, Applicants submit that one of skill in the art would have been able to ascertain the antibody encompassed by the term "MEDI-507."

The specification of the present application teaches that the amino acid sequence of LO-CD2a is disclosed in U.S. Patent Nos. 5,730,979, 5,817,311, and 5,951,983, which issued before the filing date of the present application, and incorporates these patents into the specification. *See* page 25, lines 4-7 of the specification of the present application and Figures 31 and 32 of U.S. Patent No. 5,730,979. The specification of the present application also states that the cell line producing the monoclonal antibody termed "LO-CD2a" was deposited with the ATCC as Accession No. HB 11423 on July 28, 1983. Thus, Applicants submit that one of skill in the art would have been able to ascertain the antibody encompassed by the term "LO-CD2a."

In view of the foregoing, Applicants respectfully assert that the rejection under 35 U.S.C. § 112, second paragraph, cannot stand and should be withdrawn.

II. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

A. MEDI-507 & LO-CD2a Were Obtainable

Claims 1, 3-15, 17, 23-32, and 44 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Examiner contends that MEDI-507 and LO-CD2a are required to practice the claimed methods and thus, Applicants must be show that they were known or readily available to the public or obtainable by a repeatable method set forth in the specification. In order to expedite prosecution of the present application and without conceding to the propriety of the rejection, Applicants have canceled claims 1, 3-15, 17, 23-32 and 44, without prejudice and added new claims 45-82. For the reasons below, this rejection should not be applied to new claims 45-82.

Applicants submit that the antibodies referred to as "MEDI-507" "LO-CD2a" were known and obtainable by a repeatable method. As discussed above, the amino acid sequences for MEDI-507 and LO-CD2a were available to one of skill in the art as of the effective date of the present application. *See* Example 11 and Figures 31 and 42 of Bazin, and Figures 31 and 32 of U.S. Patent No. 5,730,979. Techniques for producing MEDI-507 and LO-CD2a are described in the specification of the present application and were known to one of skill in the art as of the effective date of the present application. *See, e.g.*, page 99, line 24 to page 111, line 17 of the specification of the present application. Further, LO-CD2a is available from the ATCC as Accession No. HB 11423. Thus, Applicants respectfully assert that one of skill in the art would have been able to obtain the antibodies referred to as "MEDI-507" and "LO-CD2a."

B. Claimed Methods Are Fully Enabled

Claims 1-7 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Examiner contends that the specification does not enable one of skill in the art to use an anti-CD2 antibody to treat any cancer. In order to expedite prosecution of the present application and without conceding to the propriety of the rejection, claims 1-7 have been canceled, without prejudice and new claims 45-82 have been added. The new claims are directed to methods of treating a non-cutaneous

T-cell malignancy by administering an anti-CD2 antibody, such as MEDI-507 or an antigen-binding fragment thereof, or an antibody that competes with MEDI-507 for binding to human CD2. Thus, the claim amendments render the rejection moot. Accordingly, the rejection cannot stand and should be withdrawn.

III. THE REJECTION UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 1, 6, 7, 26-31, 33-37, 39, 40, 62, 63, 66 and 69 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bazin in view of White et al., 1989, Journal of Clinical Pathology 42(4): 403-408 ("White"), Lin et al., 1994, Medical and Pediatric Oncology 23(1): 26-35 ("Lin I), Au et al., 2002, Curr. Oncol. Rep. 4(5): 434-442 ("Au"), Neville et al., U.S. Publication No. 2004/0127682 ("Neville"), Doronina et al., U.S. Publication No. 2003/0083263 ("Doronina"), Wallner et al., U.S. Patent No. 6,162,432 ("Wallner"), and Lin et al., 1996, Cell. Immunol. 167(2): 249-258 ("Lin II"). The Examiner contends that: (a) Bazin teaches a method for inhibiting the proliferation of T cells in a human comprising administering a therapeutically effective amount of MEDI-507 or an antigen-binding fragment thereof, or an antibody that immunospecifically binds to an epitope comprising amino acid residue 18, 55 or 59 or human CD2; (b) White teaches that biopsies taken from 10 of 11 patients with peripheral T cell lymphoma were positive for CD2 expression; (c) Lin I teaches that biopsies taken from 5 patients with peripheral T-cell lymphoma were all positive for CD2 and CD3 expression and that treatment of peripheral T-cell lymphoma includes combination chemotherapy; (d) Au teaches that peripheral T-cell lymphoma refers to malignant lymphoproliferation of T cells of post-thymic origin in differentiation and that it encompasses at least 8 distinct disease entities; (e) Wallner teaches a method for inhibiting T cell proliferation and activation, for example to treat cutaneous T-cell lymphoma, comprising administering a therapeutically effective amount of an anti-CD2 antibody; (f) Neville teaches the use of an anti-T-cell immunotoxin to immunodeplete T cells to treat or ameliorate cancer; (g) Doronina teaches how to conjugate a therapeutic agent or drug, such as auristatin PHE, to an antibody which binds to a tumor associated cell surface protein and is internalized; and (h) Lin II teaches that anti-CD2 and anti-CD3 antibodies induce internalization. *See* Office Action at pages 5-8. The Examiner opines that one of ordinary skill in the art would have been motivated to use the anti-CD2 antibodies of Bazin to treat peripheral T-cell disorders because Bazin teaches that the anti-CD2 antibodies effectively deplete T-cells, and White and Lin I teach that CD2 is expressed by the majority

of the tumor samples from individuals with peripheral T-cell disorders. *See* Office Action at page 9. The Examiner concludes that it would have been *prima facie* obvious to treat a peripheral T-cell lymphoma using MEDI-507 or an antigen-binding fragment thereof, or an antibody that binds to an epitope comprising amino acid residues 18, 55 or 59 of human CD2 and that one of ordinary skill in the art would have had a reasonable expectation of success.

Applicants note that the claims rejected under 35 U.S.C. § 103(a) include claims 33-37, 39 and 40 that the Examiner states on page 2 of the Office Action as being withdrawn from consideration. Applicants also note that the claims rejected under 35 U.S.C. § 103(a) include claims 62, 63, 66 and 69 which were not pending in this application prior to this Amendment. Accordingly, Applicants are going to ignore the Examiner's rejection of claims 33-37, 39, 40, 62, 63, 66 and 69.

In order to expedite prosecution of the present application and without conceding to the propriety of the rejection, claims 1-44 have been canceled, without prejudice and new claims 45-82 have been added. For the reasons below, the rejection under 35 U.S.C. § 103(a) should not be applied to new claims 45-82.

A finding of obviousness requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1996). The proper inquiry is whether the art suggests the invention, and whether the art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell* 853 F.2d 894, 7 U.S.P.Q. 2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Appellants' disclosure. *In re Vaeck* 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991).

None of the cited references, alone or in combination, teach or suggest the use of an antibody that immunospecifically binds to human CD2 to treat a human with a non-cutaneous T-cell malignancy, much less a non-cutaneous T-cell malignancy that is refractory or non-responsive to chemotherapy.

Bazin generically describes using LO-CD2a and MEDI-507 to prevent or inhibit T cell activation. In particular, Bazin describes the use of LO-CD2a and MEDI-507 for preventing or inhibiting graft rejection, graft versus host disease, and autoimmune disease. As acknowledged by the Examiner on page 6 of the Office Action, Bazin does not teach or

suggest using LO-CD2a or MEDI-507 to treat cancer, much less to treat a non-cutaneous T-cell malignancy.

The deficiencies in Bazin are not cured by the secondary references cited by the Examiner. White describes the results obtained from immunophenotyping bone marrow infiltrates obtained from 11 patients with peripheral T-cell lymphoma and discusses the value of bone marrow trephine immunophenotyping. White finds that bone marrow infiltrates from 10 out of 11 patients were CD2 positive but that the infiltrates from all 11 patients were CD3 positive. White does not teach or suggest treating a non-cutaneous T-cell malignancy by administering an anti-CD2 antibody, much less MEDI-507 or an antigen-binding fragment thereof, or an antibody that competes with MEDI-507 for binding to human CD2. In fact, White does not even teach or suggest using CD2 in the diagnosis of T-cell lymphoma. Rather, White suggests using CD3 in the diagnosis of T-cell lymphoma. In view of the teaching in White, one of skill in the art, at most, might use CD3 (not CD2) to diagnosis T-cell lymphoma.

Lin I is a case report describing the conditions and treatments for five children with peripheral T-cell lymphoma in Taiwan. Lin I states that the five children had poor responsiveness to conventional therapy for peripheral T-cell lymphoma and suggests that bone marrow transplantation in early stages of the disease might cure the disease. Lin I does not teach or suggest treating a non-cutaneous T-cell malignancy by administering an anti-CD2 antibody, much less MEDI-507 or antigen-binding fragment thereof, or an antibody that competes with MEDI-507 for binding to human CD2. In view of the teaching in Lin I, one of ordinary skill in the art might, at most, be motivated to use bone marrow transplantation to treat peripheral T-cell lymphoma.

Au merely discusses the disease entities that are classified as peripheral T-cell lymphomas. Au does not teach or suggest treating a non-cutaneous T-cell malignancy by administering an anti-CD2 antibody, much less MEDI-507, or an antigen-binding fragment thereof, or an antibody that competes with MEDI-507 for binding to human CD2.

Wallner describes methods of using inhibitors of the CD2/LFA-3 interaction to treat skin conditions characterized by increased T cell activation and abnormal antigen presentation in the dermis and epidermis of mammals. Wallner does not teach or suggest methods of treating non-cutaneous T-cell malignancies using an anti-CD2 antibody, much less using MEDI-507 or an antigen-binding fragment thereof, or an antibody that competes with MEDI-507 for binding to human CD2. Further, Wallner does not teach or suggest treating non-cutaneous T-cell malignancies that are non-responsive or refractory to

chemotherapy using an anti-CD2 antibody, much less MEDI-507 or an antigen-binding fragment thereof, or an antibody that competes with MEDI-507 for binding to human CD2.

Neville describes anti-T cell immunotoxins, in particular anti-CD3 immunotoxins, and the use of such immunotoxins in the treatment of T-cell mediated pathologies. Neville does not describe anti-CD2 immunotoxins, much less the use of anti-CD2 immunotoxins to treat non-cutaneous T-cell malignancies. Further, there is no teaching or suggestion in Neville to treat a non-cutaneous T-cell malignancy using an unconjugated anti-CD2 antibody, much less using unconjugated MEDI-507 or an antigen-binding fragment thereof, or an unconjugated antibody that competes with MEDI-507 for binding to human CD2.

Doronina describes conjugation of auristatin to an antibody, in particular anti-CD30 antibodies. Doronina does not teach or suggest conjugating auristatin to an anti-CD2 antibody, much less conjugating auristatin to MEDI-507 or an antigen-binding fragment thereof, or an antibody that competes with MEDI-507 for binding to human CD2. Moreover, there is no teaching or suggestion in Doronina to treat a non-cutaneous T-cell malignancy using an unconjugated anti-CD2 antibody, much less using unconjugated MEDI-507 or an antigen-binding fragment thereof, or an unconjugated antibody that competes with MEDI-507 for binding to human CD2.

Lin II describes the effect of an anti-CD2 antibody and/or an anti-CD3 antibody on the expression of CD2 and CD3 by murine T lymphocytes *in vitro*. Lin II does not teach or suggest methods of treating non-cutaneous T-cell malignancies using an anti-CD2 antibody, much less using MEDI-507 or an antigen-binding fragment thereof, or an antibody that competes with MEDI-507 for binding to human CD2.

Accordingly, the deficiency in Bazin is not cured by the seven (7) secondary references cited by the Examiner.[1] The combination of Bazin and the secondary references do not teach or suggest methods of treating non-cutaneous T-cell malignancies using an anti-CD2 antibody, much less using MEDI-507 or an antigen-binding fragment thereof, or an antibody that competes with MEDI-507 for binding to human CD2.

There is no suggestion or motivation to modify the cited references to administer an anti-CD2 antibody, such as MEDI-507 or an antigen-binding fragment thereof, or an antibody that competes with MEDI-507 for binding to human CD2, to treat a non-cutaneous T-cell malignancy. The Examiner is improperly relying on hindsight reasoning obtained from the specification of the present application to arrive at the claimed invention. It is

[1] The Examiner's citation of a total of eight references to reject the claims as obvious indicates the weakness of the Examiner's position.

impermissible to engage in hindsight reasoning, using the claims as a frame and the prior art reference as a mosaic to piece together a facsimile of the claimed invention. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.* 220 USPQ 303, 312 (Fed. Cir. 1983).

Further, one of ordinary skill in the art would not have had a reasonable expectation of success based upon the teaching in the cited references because the disease entities described in the cited references are different from the non-cutaneous T-cell malignancies of the claimed invention. Graft rejection, graft versus host disease, autoimmune diseases, and the skin conditions of Wallner have different pathologies and manifest different symptoms than the non-cutaneous T-cell malignancies of the claimed invention. None of the cited references have an example which would lead one of ordinary skill in the art to conclude that there would be a reasonable expectation of success in treating a non-cutaneous T-cell malignancy in a human by administering an anti-CD2 antibody.

In view of the foregoing, the rejection under 35 U.S.C. § 103(a) cannot stand and should be withdrawn.

CONCLUSION

Applicants believe that the present claims meet all of the requirements for patentability. Consideration and entry of the foregoing amendments and remarks into the file of the present application is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

Respectfully submitted,

Date: March 26, 2007

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